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Efficacy and safety of a rapid intravenous injection of ketamine 0.5 mg/kg in treatment-resistant major depression: an open 4-week longitudinal study

Running title: Bolus of Ketamine in depression

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Abstract

Background: Ketamine has been documented for its rapid antidepressant effects. However, optimal dose and delivery route have not yet been thoroughly investigated. The objectives of this study were to document the safety and test the antidepressant and anti-suicidal effects of a single rapid 1-minute injection of ketamine 0.5 mg/kg in treatment-resistant depression (TRD). **Methods:** Ten patients with TRD were included in an open, non-controlled 4-week study and received a rapid intravenous dose of ketamine 0.5 mg/kg. Main outcome measure was the Montgomery-Åsberg Depression Rating Scale (MADRS) and suicidality was assessed using the Scale for Suicide Ideation. **Results:** Rapid injection of ketamine elicited transient increase of blood pressure and altered states of consciousness in all patients and mild psychotomimetic effects in 4 patients, which all resolved without any intervention. Decrease of depression severity was observed from 40 min post-injection until day 15. Eight patients became responders within 1 day and all were non-responders after 4 weeks. The decrease of suicidal ideation was significant until day 7. Analysis indicated that higher severity of depression and anxiety at baseline predicted a larger MADRS decrease after 4 weeks. **Conclusions:** This study suggests that in well-controlled medical settings with adequate monitoring, a single rapid 1-minute injection of ketamine 0.5 mg/kg can be well tolerated and is efficacious in rapidly reducing depression symptoms and suicidal thoughts in outpatients with TRD. These findings are relevant to the practice of general clinical psychiatry and emergency departments *were ketamine can have a place in acute management of TRD*. Larger studies are necessary to confirm these results.

Introduction

The action of most antidepressant drugs relies on the modulation of serotonergic, noradrenergic and/or dopaminergic neurotransmission [1]. However, treatment resistance and delayed response remain major challenges in antidepressant therapy. Two to four weeks are needed to evaluate treatment response and at least 30% of patients do not respond adequately to a first-line treatment [2]. Treatment options for partial- and non-responders include switching to another antidepressant, combining antidepressants or augmenting antidepressant therapy with psychotherapy, other drugs (e.g. antipsychotics) or electroconvulsive therapy (ECT) [2-4].

In recent years, one of the most promising approaches to overcome the drawbacks of antidepressant therapy has been to target glutamatergic neurotransmission [5]. Ketamine is a potent non-competitive glutamatergic N-methyl-D-aspartate (NMDA) antagonist [6].

Synthesized in the early 1960s, it has been introduced as an anesthetic agent in the 1970s. More recently, ketamine has demonstrated rapid antidepressant efficacy and raised hope for patients with refractory mood disorders. However, the emergence of dissociative side effects, such as hallucinations and altered sensory state, has limited its clinical use and led to its recreational misuse as a party drug [7]. Increased off-label use and risk of abuse have raised ethical concerns and prompted for guidance on ketamine use in mood disorders [8,9].

The first study documenting the rapid antidepressant effect of ketamine was a small randomized placebo-controlled crossover trial published in 2000 [10]. Wider interest arose after confirmation of these results in a larger study with 18 patients [11]. Subsequently, many case studies, prospective open-label studies, randomized controlled trials and meta-analyses have been published, reporting a rapid and strong but transient antidepressant effect of ketamine in treatment-resistant depression (TRD) [12]. A recent systematic review and meta-analysis identified 9 randomized trials including 201 participants with either unipolar or bipolar affective disorder [13]. At the usual subanesthetic low dose (0.5 mg/kg intravenous 40-minute infusion), ketamine had larger effects than placebo from day 1 to day 7 on depression severity, response rate and remission rate, whereas suicidality was significantly reduced on days 1 to 3. It was generally well tolerated, with transient, mild-to-moderate dissociative symptoms and blood pressure and/or heart rate increases in a minority of patients. No major medical event was reported. Safety studies of subanesthetic doses of ketamine generally support a low level of risk, provided that hemodynamic changes and dissociative symptoms are monitored carefully [14,15].

Studies that investigated the dose–response relationship or optimal route of ketamine administration in TRD have been remarkably scarce so far. In most studies, 0.5 mg/kg were slowly infused intravenously (IV) over about 40 minutes. In a meta-analysis, this dosing regimen appeared more effective than lower doses of ketamine [13]. In a recent dose escalation study over 3 weeks, improvement of depression severity was more pronounced after increasing the dose from 0.5 to 0.75 mg/kg (IV over 45 min) [16]. Following recommendations in anesthesia to administer ketamine over a short 60-second period, two studies conducted in emergency departments considered rapid (1-2 min) IV injection of ketamine 0.2 mg/kg, with the objective to assess anti-suicidal effects [17,18]. In the first study including 14 depressed patients, a significant relief of suicidal ideation and depression severity was observed from 40 min post-injection to day 10, whereas two patients experienced transient mild psychotomimetic and dissociative symptoms [18]. In the second study, 49 medication-free patients were included based on subjective expression of suicidal ideations or recent suicidal actions. Even though suicidal ideation rapidly decreased after

ketamine injection, it was concluded that effect size was not large enough to be considered clinically meaningful [17].

Given that ketamine dose of 0.5 mg/kg has rapid antidepressant and anti-suicidal effects in patients with TRD, and that rapid IV injection might be a convenient and promising new route of administration in general clinical psychiatry, especially in emergency settings, the objectives of the present open-label study were three-fold:

(1) To test the antidepressant and anti-suicidal effects of a single 0.5 mg/kg 1-minute IV injection of ketamine in patients with TRD followed in a "real-life" outpatient setting;

(2) To monitor safety parameters and document dissociative effects of this route of administration;

(3) To explore whether baseline symptoms and early improvement would predict longer-term antidepressant effect, after 4 weeks.

Methods

Patients and setting

The study was conducted at the Geneva University Hospitals, Geneva, Switzerland, in accordance with local and national legislation, and the Declaration of Helsinki [19]. The study protocol was approved by the local ethics committee and registered in the clinicaltrials.gov database (NCT01135758). All patients gave written informed consent prior to any assessment.

Patients were eligible if they met the following inclusion criteria: age between 25 and 65 years; diagnosis of major depressive disorder without psychotic features, as assessed with the Structured Clinical Interview for DSM-IV® Axis I Disorders - Clinician Version (SCID I, [20]); moderate to severe depression, i.e. score of 25 or higher on the Montgomery-Åsberg Depression Rating Scale (MADRS, [21]); TRD, defined as a failure to respond to at least two drug trials with sufficient duration at the maximum authorized or tolerated dose during the current episode[22]; unchanged psychotropic medication (antidepressants, antipsychotics, mood stabilizers) during the last 6 weeks prior to inclusion. Exclusion criteria were as follows: lifetime history of psychotic symptoms or bipolar disorder; substance abuse or dependence in the previous 3 months (except nicotine); axis I psychiatric comorbidity other than anxiety disorders; serious and imminent risk of suicide (score ≥ 4 on item 10 of the MADRS); any contra-indication to the administration of ketamine.

Patients were recruited at the local department of mental health and psychiatry. Of 15 patients who provided informed consent, 10 met all eligibility criteria and received the study medication. Nine were recruited from an outpatient clinic and one at the psychiatric hospital.

Study design and ketamine administration

Twelve visits were scheduled during this single-arm, open-label study: screening, information and informed consent (1-2 weeks before ketamine administration); baseline (1 day before ketamine administration); day of ketamine administration (day 0); and days 1, 2, 3, 6, 7, 10, 15, 22 and 29 post-ketamine. During the first visit, blood samples were collected and electrolytes (Na, K, Cl, Ca), thyroid hormones (T3, TSH; if not available during the last 4 weeks), liver function (gamma-GT, ASAT, ALAT), kidney function (creatinine) and blood cell counts were assessed. A standard ECG was also recorded.

Ketamine administration and all assessments on day 0 took place at the clinical trial unit of the Geneva University Hospitals, where patients stayed for about 6 hours in order to be closely monitored for somatic and psychiatric symptoms. Patients underwent a physical examination by an experienced anesthesiologist before being administered a single sub-anesthetic IV injection of ketamine (0.5 mg/kg over 1 min). Before, during and after the injection, blood pressure, ECG and O_2 saturation were monitored. Clinical assessments were performed at 60 min before and 40, 80, 110 and 230 min post-injection. A psychiatrist was present during the entire visit.

Throughout the 4-week follow-up period, participants attended an outpatient clinic under “real life” conditions. During the first 8 days after ketamine administration, psychopharmacological treatment was kept unchanged. The only accepted adjustable comedication included clorazepate up to 30 mg/day (or equivalent) and zolpidem up to 20 mg/day (or equivalent).

Outcome measures

The primary outcome measure was the MADRS, a 10-item clinician-administered rating scale for depression severity, designed to be sensitive to change in patients treated with antidepressants [21]. We defined treatment response as a 50% or more MADRS decrease from baseline, remission as a MADRS score of 10 or less and relapse as a MADRS score of 20 or more on two consecutive occasions after day 0, i.e. severity of symptoms corresponding to moderate depression [23,24]. Additional depression rating scales included the clinician-rated 21-item Hamilton Depression Rating Scale (HDRS, [25]) and the self-rated 21-item Beck Depression Inventory (BDI-II, [26]). Each of these three scales includes an item assessing suicidality. Depression severity was assessed at each study visit and 60 min before, 40, 80, 110 and 230 min after ketamine administration on day 0.

The severity of suicidal ideation was assessed on 3 occasions (baseline, day 1 and day 7) using the clinician-rated Scale for Suicide Ideation (SSI, [27]), which provides a total score and 3 subscores for active suicidal desire, passive suicidal desire, and specific plans for suicide. Self-reported anxiety was assessed with the state section of the State-Trait Anxiety Inventory (STAI-S, [28]) and the Beck Anxiety Inventory (BAI, [29]) on the same 3 occasions. Four BAI subscales reflect neurophysiological, subjective, panic, and autonomic symptoms of anxiety.

The Brief Psychiatric Rating Scale (BPRS, [30]) was administered 5 times on day 0 and at each visit from day 1 to day 7. Its positive symptom subscale, which includes unusual thought content, conceptual disorganization, hallucinatory behavior and grandiosity, was used to monitor emergent psychotic symptoms [31].

The self-rated five-dimensional altered states of consciousness (5D-ASC) scale was used to assess patients' alterations from usual consciousness on day 0 [32]. It comprises 94 items and five primary dimensions : 'oceanic boundlessness' refers to positive emotional states associated with derealization and depersonalization; 'dread of ego dissolution' measures negative experiences and anxiety associated with derealization, depersonalization and loss of control phenomena; 'visionary restructuralization' addresses perceptual alterations, such as visual hallucinations ; 'auditory alterations' ; and 'vigilance reduction'. Table 1 summarizes timeline and assessments

Insert Table 1 here

Statistical analysis

All analyses were performed on the intent-to-treat (ITT) sample, which included all patients who received the ketamine injection (n=10). For all rating scales, missing values were imputed according to the last observation carried forward (LOCF) approach. For the primary outcome measure (MADRS), only 7 of 160 data were missing (4.4%).

Categorical variables were described using frequency tables (N, %). Because sample size was small and the normality assumption was difficult to ascertain, ordinal and continuous variables were described with median (range). Change over time was tested with the non-parametric Friedman analysis of variance for repeated measures. Post-hoc tests considered all possible differences with respect to baseline, with Bonferroni correction for multiple tests (k=15 comparisons for MADRS, HDRS and BDI-II; k=2 for SSI, STAI-S and BAI). Time to response, remission and relapse was analyzed using Kaplan–Meier survival curves. Spearman's rank correlation coefficients (r_s) were used to test the associations between baseline scores and changes on different dimensions. Statistics were computed using SPSS

version 22 (IBM corporation, Armonk, NY). All tests were two-tailed, with significance level at 0.05.

Results

Patients were enrolled between July 2010 and June 2015. Sociodemographic and clinical characteristics are displayed in table 2. All but one patient met diagnostic criteria for comorbid anxiety disorders. All patients received antidepressants throughout the study. One patient failed to complete the trial because of increased suicidality leading to hospital admission (see below), but he was included in the ITT sample.

Insert Table 2 here

MADRS depression score as a function of time is illustrated in figure 1. The global time effect was statistically significant (Friedman test, $p<0.001$). Post-hoc comparisons with baseline score (median 29, range 26-34) revealed significantly reduced depression severity as early as 40 min after ketamine injection (median 14, range 10-29 ; $p<0.001$) and up to day 15 (median 20, range 7-30 ; $p=0.029$). HDRS decrease from baseline (median 24, range 20-33) was significant from 40 min post-injection (median 13, range 9-20 ; $p=0.002$) to day 22 (median 15, range 11-20 ; $p=0.023$). The decrease of the BDI-II from baseline score (median 35, range 19-45) did not reach statistical significance beyond day 3 (median 18.5, range 2-36 ; $p=0.006$).

Insert Figure 1 here

Eight of 10 patients were responders on day 0 or day 1, and 2 remained non-responders despite a MADRS decrease larger than 40% on day 0. Five patients achieved remission by day 2. Eight patients met criteria for relapse during the 4-week observation period (6 responders and 2 non-responders). All were considered as non-responders by day 29. Kaplan–Meier survival curves are shown in figure 2. Median times to remission and relapse were 2 days and 7 days, respectively.

Insert Figure 2 here

Anxiety, as measured with the STAI-S, showed a significant but transient time effect (Friedman test, $p=0.021$; see table 3). The time effect did not reach statistical significance for the BAI total score (Friedman test, $p=0.091$), in contrast with significant decreases of subscores reflecting neurophysiological ($p=0.029$) and panic symptoms of anxiety ($p=0.020$).

The effect of ketamine on suicidality, as measured with the SSI total score, was statistically significant (Friedman test, p=0.001; see table 3). The decrease from baseline was significant on day 1 (post-hoc test, p=0.002) and day 7 (p=0.003). Likewise, the active suicidal desire subscale score decreased from baseline to day 1 (p=0.007) and day 7 (p=0.003). Suicidal thoughts measured with item 10 of the MADRS similarly decreased over time (Friedman test, p<0.001), with significant changes from baseline on days 0-6, 10 and 15 (post-hoc tests; not shown). Change in suicidal ideation (SSI total score) was significantly correlated with changes in the severity of depression (MADRS, r_s=0.85, p=0.002) and anxiety (STAI-S, r_s=0.63, p=0.049) on day 1, but not on day 7 (MADRS, r_s=0.46, p=0.19; STAI-S, r_s=0.28, p=0.44).

Insert Table 3 here

The association between baseline symptom severity and MADRS decrease on day 7 and at week 4 is documented in table 4. Higher severity of depression (HDRS, BDI-II) and anxiety (BAI) at baseline were significantly associated with larger MADRS improvement at 4 weeks after ketamine injection. Whether early changes on day 1 allowed predicting later MADRS decrease is also explored in table 4. Early improvement on day 1 (MADRS, BDI-II, STAI-S) predicted a larger MADRS decrease on day 7, but not at week 4.

Insert Table 4 here

Adverse events recorded shortly after ketamine administration (day 0) are shown in table 5. As expected, a transient increase of blood pressure occurred in all patients (median peak systolic blood pressure 172 mmHg (range 143-219); median peak diastolic blood pressure 113 mmHg (range 98-137). In one patient, blood pressure values reached 219/118 mmHg five minutes after the beginning of the injection, but rapidly decreased thereafter without the need of any emergency intervention. At 40 min after ketamine administration, blood pressure was 150/97 mmHg.

Whereas somnolence and sedation were frequently observed (6 of 10 participants), 3 patients experienced dissociative symptoms and hallucinations. According to the BPRS positive symptom subscale, a small increase of psychotic symptoms occurred in 4 patients 40-80 min post-dose, and resolved thereafter. A trend was found for an inverse association between the peak of BPRS positive symptoms and the MADRS percentage change on day 0 (r_s=−0.62, p=.056).

2 patients screamed; and one patient groaned and cried shortly after the injection. One of the patients who screamed did so for approximately two minutes, and therefore this event was

considered as moderate adverse event. The two other events were considered as mild adverse events as they lasted for very few seconds.

Large inter-individual variability was observed in the patients' subjective experience of altered states of consciousness (table 5). Whereas 6 of 7 patients had scores >50% of scale maximum for 'vigilance reduction' and 'dread of ego dissolution', frequencies were lower for 'oceanic boundlessness' (3 patients), 'visionary restructuralization' (1 patient) and 'auditory alterations' (1 patient). No significant correlation was observed between 5D-ASC dimensions and MADRS percentage change on day 0.

Insert Table 5 here

Adverse effects during the 4-week follow-up period were mild to moderate and transient, except for one serious adverse event. In one patient, severe suicidality on day 7 led to study termination and voluntary admission to the psychiatric hospital. This event was not considered to be related to study procedures, but to the course of the underlying major depressive disorder: temporary increases of suicidal ideation in this patient were known and documented.

Discussion

In this open, non-controlled longitudinal study, ketamine, a potent non-competitive glutamatergic N-methyl-D-aspartate (NMDA) antagonist documented for its rapid antidepressant effects, was administered intravenously over 1 minute to 10 patients with moderate to severe depression maintained on their usual antidepressant treatment. To our knowledge, this is the first published study to explore the effects of rapid injection of ketamine 0.5 mg/kg in TRD. The most salient results were: (1) Rapid administration elicited transient increase of blood pressure and mild psychotomimetic effects, which occurred immediately after the injection and resolved without sequelae. (2) The antidepressant effect was rapid, meaningful and statistically significant for 15 days. Eight of 10 patients became responders within 24 h, but none maintained response at 4 weeks. (3) Suicidality and anxiety scores diminished rapidly after ketamine administration. (4) More severe depression and anxiety at baseline predicted larger MADRS decrease at 4 weeks, whereas early changes immediately after ketamine injection were not predictive of 4-week antidepressant effect.

Our data support that 1-minute injection of ketamine might be a feasible alternative to the usual 40-minute infusion route if the administration is performed under the condition of a well-controlled medical setting that provide adequate hemodynamic monitoring. Indeed, while

no patient displayed any major adverse event needing clinical intervention, all study participants experienced a transient increase of blood pressure immediately after the injection, with median peaks of systolic and diastolic blood pressure (172/113 mmHg) exceeding mean values in patients slowly infused over 40 min (142/86 mmHg) [15]. In one patient, who had a BMI of 30 and suffered from mild hypercholesterolaemia, blood pressure reached 219/118 mmHg, but normalized spontaneously and rapidly without medication. These data are in agreement with a recent consensus statement, which underscores the need for close medical monitoring during and after IV administration of ketamine [8].

Other adverse effects are globally comparable with those reported in the 40 minutes infusion studies[33-34]. In keeping with previous research in patients with TRD and no history of psychosis[15], psychotic symptoms were minimal and quickly resolved. Psychotomimetic effects, as measured with the BPRS positive symptom subscale, were detected in 4 patients shortly after the injection and resolved after 110 minutes. Rapid injection of ketamine elicited large inter-individual differences in the subjective experience of altered states of consciousness, but most participants endorsed some degree of 'vigilance reduction' (changes in vigilance, alertness, and cognitive performance) and 'dread of ego dissolution' (negative experience of derealization, depersonalization, cognitive disturbance, and loss of thought and self-control). Several studies reported that the intensity of psychotomimetic or dissociative symptoms predicted a larger decrease of depression severity and sustained effects of ketamine [11,35-37]. In the present study, there was a tendency for an association between a larger MADRS decrease on the day of ketamine injection and a higher peak of BPRS positive symptoms, but no association with 5D-ASC dimensions. Because the first BPRS assessment took place 40 minutes after the injection, we cannot exclude that we missed the emergence of positive symptoms immediately after the injection, when blood concentration was maximum.

The antidepressant effect of ketamine was detected as early as 40 min after the injection and remained significant for 15 days. Eight of 10 patients became responders within 1 day after ketamine injection and 5 achieved remission by day 2. However, all patients were considered as non-responders at week 4. These results are consistent with a meaningful and rapid, yet non-persistent antidepressant effect, as summarized in a recent meta-analysis. When compared to placebo, ketamine effect on depression severity peaked at day 1 and lost superiority by days 10–12, whereas response rate was significantly increased up to day 7 [38].

Literature about the pharmacological treatment of depression generally indicates that higher depression severity at baseline and early onset of improvement can be regarded as predictors of later response [39]. Yet, few studies have addressed these issues for ketamine. In

a large study of potential demographic and clinical predictors of response to ketamine in patients with TRD, baseline depression severity did not correlate with HDRS decrease at days 1 and 7 [40]. In a later report by the same group, early MADRS decrease at 230 min and one day post-infusion was identified as a significant predictor of response at 2 weeks [36]. In the present study, higher depression severity at baseline was significantly associated with larger improvement at 4 weeks post-injection. Early improvement on day 1 predicted larger effects at one week, but not at 4 weeks after administration. These results prompt for distinguishing between acute and prolonged effects of ketamine and investigating their specific predictors over an extended time frame, in order to better identify patients who would most likely benefit from ketamine treatment.

It is important to mention that all but one patient in our sample met diagnostic criteria for comorbid anxiety disorders and all had concomitant benzodiazepine treatment. On the one hand, benzodiazepine use could potentially attenuate ketamine antidepressant effects [41]. On the other hand, anxious depression predicted a better response and a longer time to relapse than non-anxious depression over a 4-week follow-up period [42]. The present study provides support to that finding, by showing that more severe baseline anxiety, as measured with the BAI, was associated with larger depression decrease 4 weeks after ketamine injection.

Ketamine has attracted considerable interest for the rapid treatment of patients at risk for suicide[42] or acutely suicidal[44]. In our sample, a single injection of 0.5 mg/kg ketamine induced a rapid anti-suicidal action that persisted up to day 7, especially on active suicidal desire as measured with the SSI. Interestingly, the decrease in suicidal ideation was significantly correlated with decreases in the severity of depression and anxiety on day 1, but not on day 7 post-ketamine. These results are consistent with those of Ballard and colleagues, who found the effect of ketamine on suicidal thoughts to be related to reductions in depressive and anxiety symptoms, but not fully explained by such effects[45]. It was recently postulated that ketamine effects on suicidality might depend on procognitive mechanisms in subgroups of individuals with deficits in cognitive function (e.g. executive function and impulsivity)[46].

The present study has several important limitations that need to be pointed out. First, statistical power was limited, due to small sample size and relatively stringent inclusion and exclusion criteria. Second, the study did not include a comparison group, for example patients treated with the usual 40-minute IV infusion method, and thus did not allow determining whether observed effects were specific to the short 1-minute injection of ketamine. Third, all patients were maintained on their previous medication when ketamine was introduced, so that heterogeneity of concomitant drug treatment might have influenced

clinical outcome. Fourth, the sample did not include acutely suicidal patients, whereas most had comorbid anxiety disorders, precluding generalization of results to other populations.

Finally, the validity of the LOCF approach might be criticized. However, the number of missing values was small. Furthermore, a major bias in the estimated effect was unlikely, because 5 of 7 missing data occurred in a single patient who had stable MADRS scores above 20 up to day 7, before terminating the study due to increased suicidality and hospital admission.

In conclusion, this study provides preliminary data suggesting that a single rapid 1-minute injection of ketamine 0.5 mg/kg in well-controlled medical settings with adequate monitoring can be well tolerated and is efficacious in reducing depression symptoms, anxiety symptoms and suicidal thoughts in outpatients with TRD, who often present a chronic, complex and challenging picture in routine clinical practice. Additional studies will be needed to compare alternative dose regimen, formulations and delivery routes and identify factors associated with favorable short- and long-term outcome.

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Table 1: Timeline and Assessments

1-2 weeks before injection	**Baseline (Day -1)**	**Injection (-60 ; +40 ; +80 ; +110 ; +230 min)**	**Day 1**	**Days 2, 3 and 6**	**Day 7**	**Days 10, 15, 22 and 29**
ELIGIBILITY	Psy status MADRS BDI-II HDRS SSI BAI STAI-S	Psy status MADRS BDI-II HDRS Side effects BPRS 5D-ASC	Psy status MADRS BDI-II HDRS Side effects BPRS SSI BAI STAI-S	Psy status MADRS BDI-II HDRS Side effects BPRS	Psy status MADRS BDI-II HDRS Side effects BPRS SSI BAI STAI-S	Psy status MADRS BDI-II HDRS Side effects

Abbreviations: MADRS, Montgomery-Åsberg Depression Rating Scale; BDI-II, Beck Depression Inventory; HDRS, Hamilton Depression Rating Scale; BPRS, Brief Psychiatric Rating Scale; 5D-ASC, five-dimensional Altered States of Consciousness scale; SSI, Scale for Suicide Ideation; BAI, Beck Anxiety Inventory; STAI-S, State-Trait Anxiety Inventory (state section).

Table 2 : Sociodemographic and clinical characteristics (n=10 patients)

		Number of patients / median (range)
Sociodemographic parameters	Female	6
	Age (years)	51 (38-58)
	Education (years)	14 (9-18)
	Married	4
	Currently unemployed	9
	Living alone	3
Psychiatric diagnosis (DSM-V code)	Major depressive disorder, recurrent, severe without psychotic features (296.33)	9
	Major depressive disorder, single episode, severe without psychotic features (296.23)	1
	Persistent depressive disorder (300.4)	8
	Anxiety disorders	9
	Social anxiety disorder (300.23)	2
	Specific phobia (300.29)	1
	Panic disorder (300.01)	4
	Generalized anxiety disorder (300.02)	4
	Obsessive-compulsive disorder (300.3)	1
	Posttraumatic stress disorder (309.81)	1
	Unspecified anxiety disorder (300.00)	1
History of illness	Age of onset (years)	27 (18-51)
	Duration of major depressive disorder (years)	21 (4-29)
	Number of major depressive episodes	3 (1-5)
	Prior suicide attempt	4
Current depressive episode	Episode duration (months)	47 (9-204)
	Hospitalization during current episode	6
	Psychotropic medication	
	Antidepressants	10
	Antipsychotics	7
	Mood stabilizers	5
	Benzodiazepines	10

Abbreviations: DSM-V, Diagnostic and Statistical Manual of Mental Disorders, 5th edition

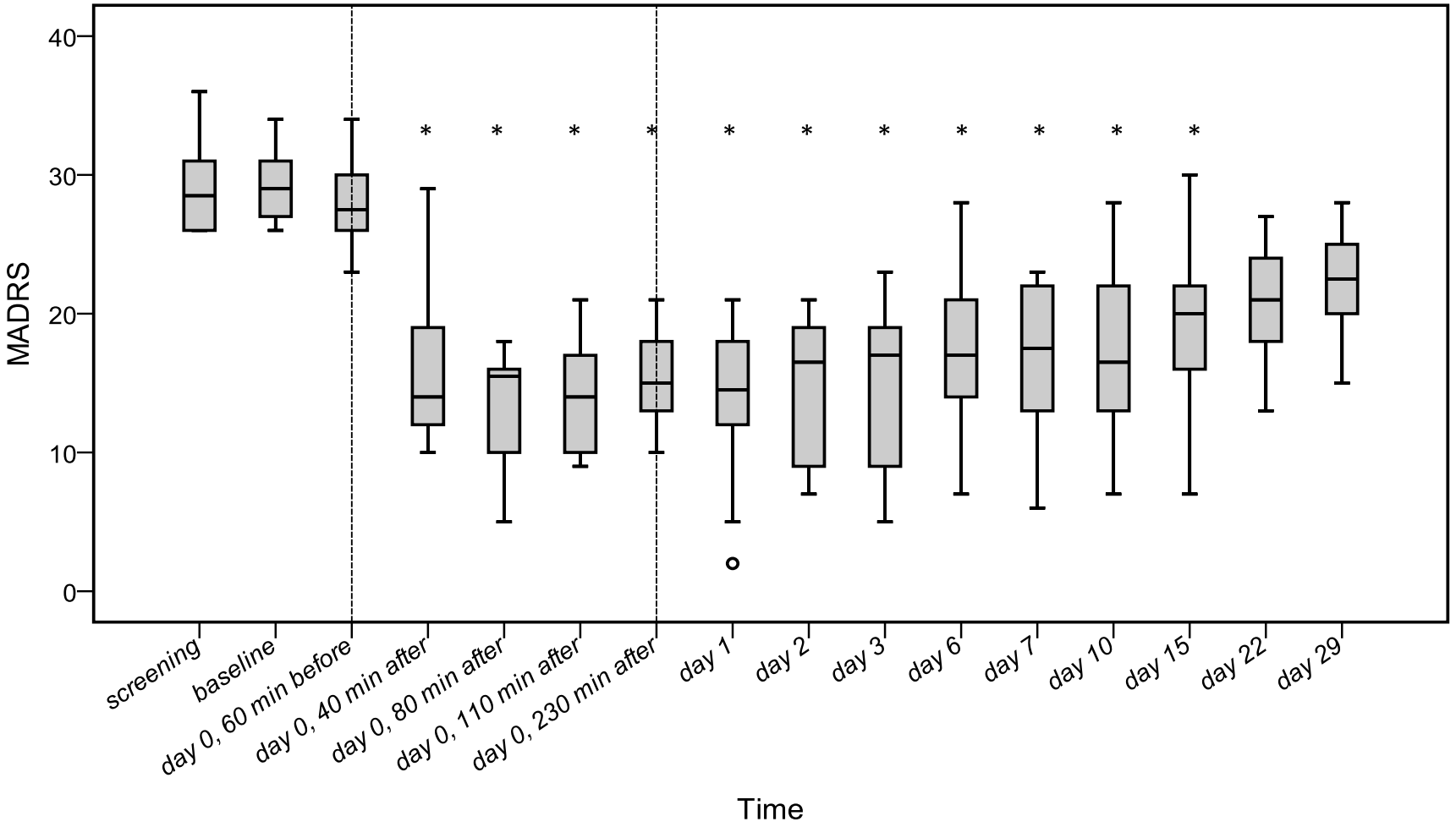

Figure 1: Depression severity (MADRS) as a function of time in 10 patients who received a single, 1-minute injection of ketamine 0.5 mg/kg (day 0). The line in the middle of the box represents the median. The lower and upper edges of the box are the 1st and 3rd quartile, respectively. The whiskers extend to the nearest value not exceeding 1.5 times the interquartile range (O depict outliers). Significant differences with respect to baseline (✱) refer to post-hoc tests (Bonferroni correction; k=15 tests) following Friedman analysis of variance ($p<0.001$).

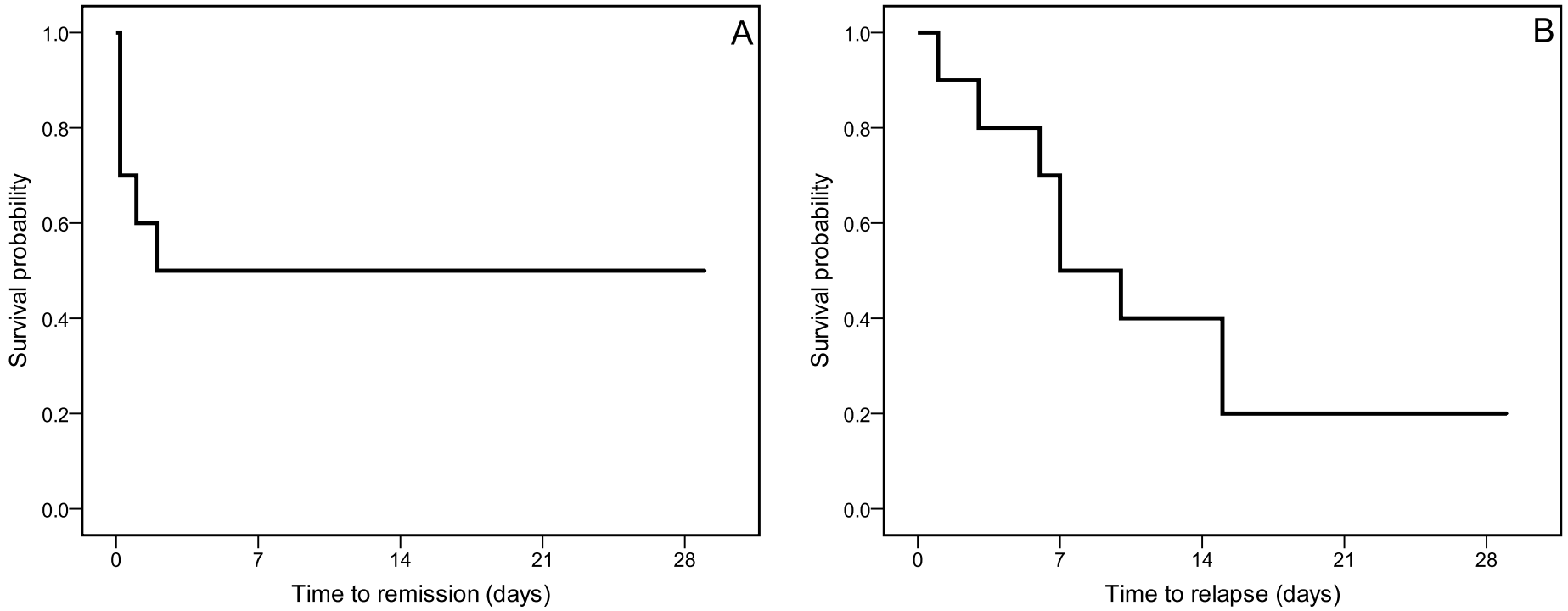

Figure 2: Kaplan–Meier survival curves for the cumulative proportions of patients not showing remission (MADRS ≤10; Part A) or relapse (MADRS ≥20 on two consecutive visits; Part B) after a single, 1-minute injection of ketamine 0.5 mg/kg. Median times to remission and relapse were 2 days and 7 days, respectively.

Table 3: Severity of depression, suicidal ideation and anxiety as a function of time (n=10 patients)

	Baseline		Day 1			Day 7			Day 29			Time effect
	Median	Range	Median	Range	$p_{adjusted}$ [b]	Median	Range	$p_{adjusted}$ [b]	Median	Range	$p_{adjusted}$ [b]	p [a]
MADRS	29	26-34	14.5	2-21	<0.001	17.5	6-23	0.010	22.5	15-28	1	<0.001
HDRS	24	20-33	11.5	2-17	<0.001	12.5	4-20	<0.001	16.5	11-22	0.55	<0.001
BDI-II	35	19-43	21	8-35	0.054	23	6-34	0.16	27.5	19-48	1	<0.001
SSI Total	12.5	3-27	8.5	0-18	0.002	3.5	0-26	0.003				0.001
Active suicidal desire	9.5	3-17	4.5	0-10	0.007	2	0-12	0.003				0.001
Passive suicidal desire	1	0-5	1	0-4	nt	0	0-4	nt				0.25
Preparation	1	0-5	0.5	0-4	nt	0	0-6	nt				0.55
Suicidal thoughts (MADRS item 10)	2	1-3	0	0-2	0.003	1	0-2	0.19	1	0-3	0.77	<0.001
STAI-S	51.5	41-77	42.5	20-71	0.067	51.5	29-73	1				0.021
BAI Total	18.5	6-41	6.5	3-23	nt	8.5	4-12	nt				0.091
Subjective	7	1-16	3	0-10	nt	3.5	1-7	nt				0.21
Neurophysio-logical	4	1-15	2	0-4	0.051	1	0-5	0.067				0.029
Autonomic	4.5	0-8	2	0-8	nt	1.5	0-4	nt				0.13
Panic	3	0-6	1	0-3	0.038	1	0-2	0.19				0.020

[a] Friedman test for overall change over time

[b] Post-hoc comparison with baseline value, p-values adjusted for multiple tests (k=15 for MADRS, HDRS and BDI-II; k=2 for SSI, STAI-S and BAI). Not tested (nt) if overall time effect was not significant

Abbreviations: MADRS, Montgomery-Åsberg Depression Rating Scale; HDRS, Hamilton Depression Rating Scale; BDI-II, Beck Depression Inventory; SSI, Scale for Suicide Ideation; STAI-S, State-Trait Anxiety Inventory (state section); BAI, Beck Anxiety Inventory

Table 4: MADRS decrease on day 7 and at study endpoint as a function of baseline symptoms and early improvement (n=10 patients)

	MADRS Percent decrease on day 7		MADRS Percent decrease on day 29	
	Spearman correlation (r_s)	p	Spearman correlation (r_s)	p
Baseline				
MADRS	0.61	0.061	0.23	0.53
HDRS	0.40	0.25	0.64	0.044
BDI-II	0.57	0.085	0.69	0.026
SSI Total	0.24	0.51	0.40	0.25
STAI-S	0.21	0.57	0.40	0.25
BAI Total	0.56	0.093	0.69	0.029
Percent decrease on day 1				
MADRS	0.67	0.036	0.26	0.47
HDRS	0.47	0.17	0.24	0.51
BDI-II	0.82	0.004	0.21	0.56
SSI Total	0.48	0.16	-0.10	0.79
STAI-S	0.64	0.047	0.46	0.19
BAI Total	0.55	0.10	0.42	0.23

Abbreviations: MADRS, Montgomery-Åsberg Depression Rating Scale; HDRS, Hamilton Depression Rating Scale; BDI-II, Beck Depression Inventory; SSI, Scale for Suicide Ideation; STAI-S, State-Trait Anxiety Inventory (state section); BAI, Beck Anxiety Inventory

Table 5: Adverse events, psychotomimetic effects and altered states of consciousness on ketamine injection day (n=10 patients)

	Number of patients / median (range)
Adverse events	
Increased blood pressure (SBP > 140 and DBP > 90)	10
Heart rate > 100	4
Somnolence, sedation	6
Dizziness	3
Dissociative state, depersonalization, hallucinations	3
Screaming, crying, groaning	3
Hyperventilation	2
Headache	2
Anxiety	2
Feeling paralyzed, « stoned »	2
Inner tension	1
Blurred vision	1
Heavy head feeling	1
Reduced sensory perception	1
BPRS peak change	0 (0-3)
Altered states of consciousness (5D-ASC) [a]	
Oceanic boundlessness (%)	49 (7-75)
Dread of ego dissolution (%)	58 (10-78)
Visionary restructuralization (%)	32 (2-83)
Auditory alterations (%)	27 (9-59)
Vigilance reduction (%)	60 (25-95)

[a] Percent of scale maximum; n=7 patients

Abbreviations: SBP, systolic blood pressure ; DBP, diastolic blood pressure ; BPRS, Brief Psychiatric Rating Scale; 5D-ASC, five-dimensional Altered States of Consciousness scale